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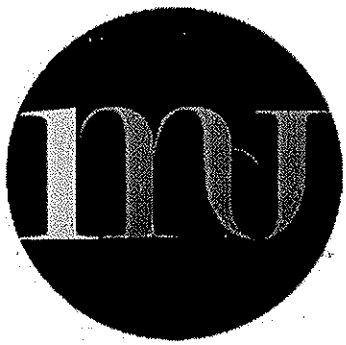
"Environment-friendly methods for the synthesis of biodynamic heterocycles"



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SYNOPSIS SUBMITTED

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DECLARATION

I hereby declare that the synopsis entitled "**Environment-friendly methods for the synthesis of biodynamic heterocycles**" is my own original work and it has not formed the basis for the award of any degree, diploma, associateship or fellowship of similar other titles.

07/05/19

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Title of the Research:

"Environment-friendly methods for the synthesis of biodynamic heterocycles"

INTRODUCTION

Green chemistry is necessary to reduce the environmental impact of manmade materials and the processes used to produce them. With the help of all the valuable ideology of green chemistry, scientists and chemists can considerably reduce the risk to the environment and human health Green chemistry principles can be attained by using environmentally safe, nontoxic, repeatable solvents and catalysts in medication manufacture and research. Heterocycles are the most diverse group of organic molecules in terms of chemical, biological, and industrial importance. They're also among the most common scaffolds in a variety of medications and pharmaceuticals-related chemicals. The work will be beneficial for economical and ecological concern. Due to short reaction time, operational simplicity, expanded reaction range, developed methodologies can be used for production of higher number of novel chemical entities. New medicinally important heterocyclic compounds will be synthesized under the framework of green chemistry. Our methodologies are a good option to obtain medicinally important compounds in quantitative yield in simple and efficient manner. This is the significant contribution to the area of research. Under the framework of green chemistry we are synthesizing wide variety of biologically and industrially significant heterocyclic scaffolds. There is a remarkable improvement over the conventional synthesis favoring atom economy and leads to reduction in time with several advantages of ecofriendly approach. Heterocyclic compounds will be synthesized using (1) water as green solvent (2) montmorillonite K10, KSF, acidic/basic and neutral alumina as inorganic solid supports (3) FeO / MgO/ CaO as efficient ecofriendly catalyst under conventional and microwave irradiation (4) lemon juice as natural catalyst. The reaction conditions will be studied and compared with conventional methods in terms of reaction time, and yield. The versatility of these techniques has been explored in terms of their synthetic utility for biologically active heterocycles. The compounds synthesized will be evaluated for their antifungal, antibacterial, anticancer, anti-inflammatory and analgesic activities. The development of effective paths to a variety of heterocycles is a fascinating field of study. Because of their fascinating characteristics, nitrogen-based compounds have become more prevalent as sub-units

in numerous medicines and agrochemical goods. Nano-sized inorganic particles, whether simple or complex, have unique physical and chemical properties, and are becoming a more important material in the creation of new nanodevices for a variety of physical, biological, medicinal, and pharmacological applications. Because of their ability to deliver medications in the optimal dosage range, nanoparticles have received increasing interest from every discipline of medicine, often resulting in higher therapeutic efficiency, decreased adverse effects, and improved patient compliance

Objectives of the study:

- To study various tools of Green Chemistry for environ-economic synthesis of some O, N, and S containing bioactive heterocyclic compounds.
- To synthesize Iron, Calcium and Magnesium Nanoparticles by using plant extracts.
- To prepare the spiro indole derivatives by using grindstone technique.
- To synthesize 4H-benzo[b]pyran derivatives and Biginelli compounds by using nanoparticles as catalyst.
- Characterisation of synthesized compounds using spectral and analytical methods.

Review of literature:

Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry.[1] About one half of over six million compounds recorded in *Chemical Abstracts* are heterocyclic.

Heterocyclic compounds play a vital role in biological processes and are widely distributed in nature, particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haemoglobin and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Heterocyclic compounds also occupy key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity. Majority of the large number of drugs being introduced in pharmacopoeia in recent years viz., chlordiazepoxide

(tranquillizer),[2] imipromine (antidepressant),[3] guanethidine (antihypertensive),[4] indapamide (diuretic and antihypertensive),[5,6] etc. are heterocyclic compounds. Many non-steroidal drugs such as ketoprofen, [7] fenoprofen and flurbiprofen[8] are well known anti-inflammatory agents; these derivatives were found to be more potent with fewer side effects. Many antibiotics including penicillin, cephalosporin, norfloxacin, streptomycin etc., also contain heterocyclic ring.[9-13] Therefore the chemistry of heterocycles is considered to be one of the most dynamic and challenging area of chemistry embracing a vast spectrum of advances of both theoretical and practical relevance. We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be: (1) a qualitative or quantitative improvement in activity, (2) a partial or total absence of undesirable side effects, (3) a lower toxicity, (4) more nutritive value, (5) improved stability and (6) a decrease in production cost. Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in generally stable. Those with two heteroatoms are more likely to occur as reactive intermediates. In recent decades, there has been an explosion of activity in the chemistry of nitrogen, oxygen and sulphur containing heterocycles such as indole, pyrazoles, benzoxazoles, triazoles, triazine, dihydropyrimidinones, thiazoles, indazoles, benzooxazepins, quinolines, thiophene, flavones, benzopyran, tetrahydropyran derivatives, [14-21] etc. They deserve a special mention due to their versatile use in pharmacological and biochemical studies as they not only display interesting chemistry as individual ring system but may also lead to a large number of new fascinating ring systems by incorporating more than one moiety leading to a variety of structural patterns.

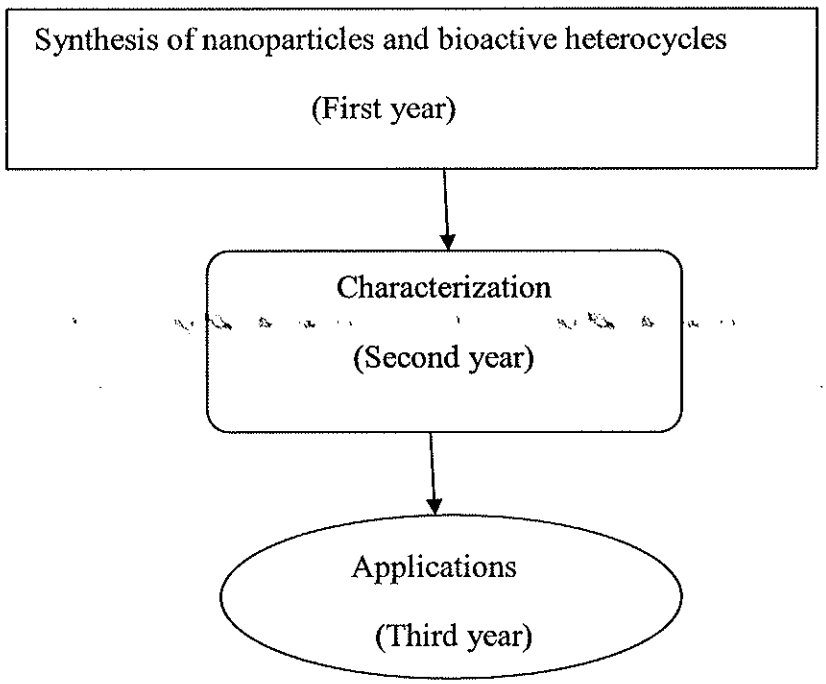
Research gaps:

The Need for Green Chemistry –Green chemistry[22-23] is the design of chemical products and process that reduce by products, waste produced and lowering of energy costs. Green technologies are one of the highest priorities for today's chemists. It provides a technical solution to many environmental problems. The most important goal for chemists is to ensure that the next generation of synthetic protocols for drugs and fine chemical synthesis is more sustainable, fully protected for human health and environmental protection, easily recycled reagent and fully greener than the current generation. In recent years the use of microwave heating[24] in synthesis of organic compounds becomes a new trend because most of the thermally driven organic chemicals reactions can be accelerated by microwave. Using such

non-conventional reaction has advantages of increase yield, short reaction time, selectivity in reaction, cleaner reaction, ease of reaction work up and eco- friendliness as compared to conventional reaction. Thus, microwave assisted synthesis become a part of green chemistry as the developed procedures are both environmentally and economically acceptable.

Methodology: The proposed work will be carried out in three parts.

- Synthesis
- Characterization



Year-wise Plan of work:

Synthesis of Green Nanocatalysts and bioactive heterocycles (First year)

Part1: Synthesis of Green Nanocatalysts: Synthesis of Green Nanocatalysts: Plant extracts will be used to synthesise different nanoparticles (green methods).

1. Calcium oxide Nanoparticles

Method:

(i) Preparation of extract from Papaya leaves: 100 g of well washed papaya leaves were used to make papaya extract. It was then cooked for half an hour in 200 mL distilled water, filtered with Whatmann no 1 filter paper, and the resulting extract was chilled before being utilised to make metal oxide nanoparticles.

(ii) Synthesis of calcium oxide nanoparticles using plant extracts

2. Iron oxide Nanoparticles: 3. Magnesium oxide Nanoparticles: 4. Zinc oxide Nanoparticles

Chapter-1: Review based on Tools of Green Chemistry for environ-economic synthesis of heterocyclic compounds.

In this review, activity in the area of greener synthetic transformations which use grindstone technology and microwave irradiation or using aqueous medium or supported reagents or nanocatalysts / natural catalyst for the synthesis of some O, N, and S containing bioactive heterocyclic compounds has been described.

Tools of Green Chemistry

1. Organic synthesis in water: Powerful tool of Green Chemistry

2 Catalysis: An important tool of green chemistry (i) Nanocatalysts (ii) Green Catalysts (iii) Biocatalysts

3 Grindstone Chemistry Technique: A simplified green chemistry approach

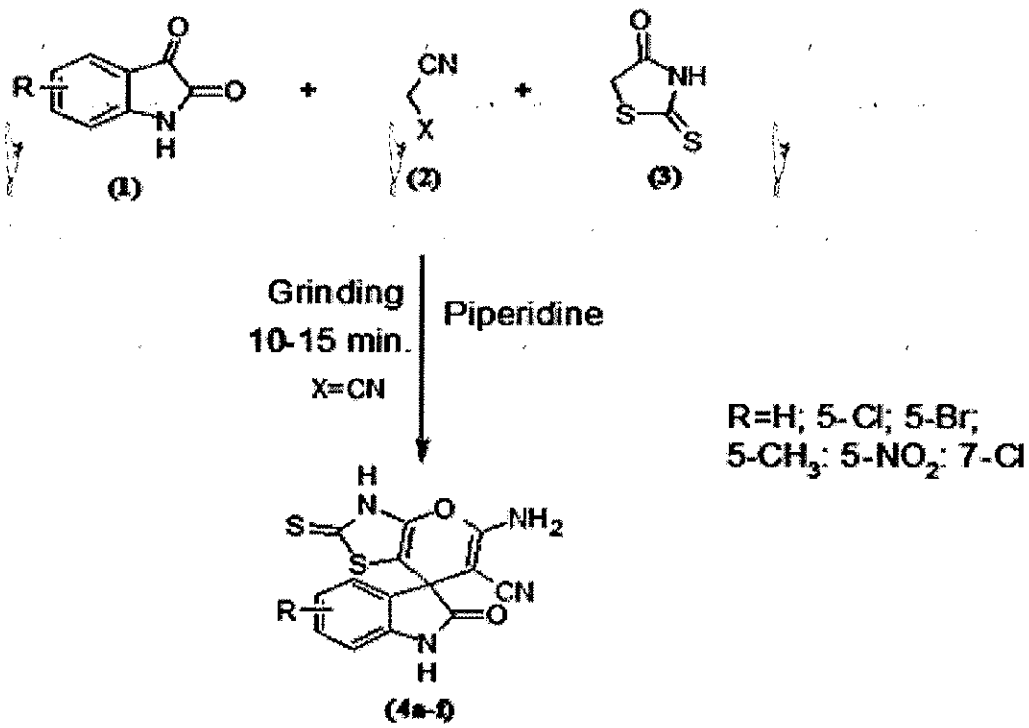
4 Microwave Syntheses: A Potential Tool of Green Chemistry

Chapter-2: Green synthesis of Iron, Calcium and Magnesium nanoparticles using plant extracts.

- The use of plant extracts in the synthesis of nanoparticles have proven to be cost effective and opens up a wide area in non-toxic nanoparticle synthesis.
- Iron, Calcium and Magnesium Nanoparticles were synthesized successfully in an easy and less time consuming way using Camellia Sinensis leaves extract (Green tea), Papaya leaves extract and aloevera leaves extract respectively.

Chapter-3: Green preparation and structure elucidation of spiro indole derivatives using grindstone technique.

- Grindstone Chemistry technique will be applied for conducting multicomponent reaction of 1H-indole-2,3-dione, malononitrile and 2-thioxo-4-thiazolidinone for the synthesis of Spiro indole derivatives.



Chapter-4: Microwave assisted synthesis of 4H-benzo[b]pyran derivatives by MgO nanoparticles.

MgO is of great interest to many scientists in recent years as an effective catalyst in green synthetic organic chemistry. As part of our work on one-pot multicomponent reactions catalyzed by metal nanoparticles herein, we report the one pot synthesis of multicomponent condensation of aldehyde **1** (1 mmol), malononitrile **2** (1mmol), meldrum's acid **3** (1 mmol) in presence of MgO nanoparticles (50 mg) under solvent free condition which enhance their efficiency from an economic as well as a green point of view.

Chapter-5: Nanomaterials catalyzed green chemical synthesis of Biginelli compounds.

- The 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPM's) have recently emerged as important target molecules due to their therapeutic and pharmacological properties. As part of our work on one-pot multicomponent reactions catalyzed by metal nanoparticles herein, we report the one pot synthesis of component

condensation of aromatic aldehyde (1), malononitrile (2) and Urea (3) in the presence of FeO nanoparticles (30mg) under solvent free condition which enhance their efficiency from an economic as well as a green point of view.

Chapter-6: Synthesis and characterization of various rhodanine derivatives in aqueous medium.

Compounds containing rhodanine framework possess diverse biological activities such as anti-inflamatory, antimalarial, and antibacterial activity. Due to high potential of rhodanine derivatives in drug discovery, there is growing interest to devise a rapid and clean method for their synthesis. This developed procedure offers several advantages including high yield, mild reaction conditions, and environmental friendliness.

Significance of Work:

For the synthesis of O, N, and S containing heterocyclic compounds, new environmentally friendly techniques have been established. The operational simplicity, environmentally friendly circumstances, and high yield obtained in a quick reaction time are the main advantages that meet the requirements of green production, including energy savings and high efficiency. This is an important contribution to the field of study. The work will benefit the pharmaceutical industry and will be essential for both economic and environmental concerns. Because of the fast reaction time, operational simplicity, wider reaction range, and reusability of catalyst developed techniques, a greater number of unique chemical entities with enhanced biological activity can be produced. The produced chemicals have been proven to be very effective at inhibiting microorganism growth. They can be employed as ligands to help metal complexes develop.

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